ORIGINAL RESEARCH ARTICLE

Serum CD40 ligand düzeyi ile tek başına ısrarcı atriyum fibrilasyonu ilişkisi

Relationship between serum level of CD40 ligand and persistent lone atrial fibrillation

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ÖZET

Amaç: Enfamasyonun atriyum fibrilasyonu (AF) patogenezinde rol oynadığı düşünülmektedir. Protrombotik ve proenflamatuvar bir molekül olan CD40 ligand (CD40L) ile tek başına AF arasında ilişki daha önce araştırılmamıştır. Çalışmamızda bu ilişki yanında serum CD40L düzeyinin sağlıklı bireylerle tek başına AF'li hastaları ayırt etmedeki rolü de incelenmiştir.
Yöntemler: Çalışmaya tek başına ısrarcı AF'si olan 35 hasta ve kontrol grubu olarak 30 sağlıklı birey alındı. Çalışmaya alınan bütün olgularda serum CD40L ve yüksek duyarlıklı C-reaktif protein (hs-CRP) seviyeleri ölçüldü. Tüm katılımcılara transtorasik ekokardiyograf yapıldı.
Bulgular: Tek başına ısrarcı AF grubunda ortalama serum CD40L, hs-CRP, sol ventrikül diyastol sonu çap ve sol atriyum çap değerleri kontrol grubuna göre istatistiksel olarak anlamlı yüksek bulundu (sırasıyla, 7.4±3.5 ng/mL ve 4.3±1.2 ng/mL, p<0.0001; 3.7±1.6 mg/L ve 1.7±0.8 mg/L, p<0.0001; 53.0±4.2 mm ve 46.0±3.8, p<0.0001; 43.5±3.5 mm ve 33.7±3.5, p<0.0001). Spearman korelasyon analizi serum CD40L düzeyleri ile sol atriyum çapı (r=0.81, p<0.0001) ve hs-CRP düzeyleri (r=0.72, p<0.0001) arasında pozitif korelasyon olduğunu gösterdi. ROC (receiver operating curve) analizinde tek başına AF grubu ile sağlıklı kontrol grubunun ayrımında serum CD40L düzeyinin anlamlı etkinliği saptanarak uygun eşik değer >4.5 ng/mL olarak bulundu (eğri altında kalan alan: 0.847, %95 güven aralığında: 0.759–0.934; p<0.0001).
Sonuç: Çalışmamızın bulguları serum CD40 ligand seviyesinin tek başına AF gelişiminde önemli rol oynadığına işaret etmektedir. Tek başına AF'li hastalarda yüksek CD40L seviyelerinin yüksek tespit edilmesi bu hastaların kardiyovasküler hastalıklar açısından yakından takip edilmesi gerekliliğini düşündürmektedir.

ABSTRACT

Objective: Infammation is thought to play a role in the pathogenesis of atrial fbrillation. The relationship between CD40 ligand (CD40L), a prothrombotic and proinfammatory molecule, and lone atrial fbrillation was presently investigated for the first time. Levels of serum CD40L were also tested, regarding its role to distinguish patients with lone atrial fibrillation from healthy individuals.
Methods: Presently 35 patients with lone persistent atrial fİbrillation and a control group of 30 healthy individuals. were included in the study. Serum levels of CD40L and high-sensitive C-reactive protein (hs-CRP) were measured, and transthoracic echocardiography was performed on all participants.
Results: Mean serum CD40L, hs-CRP, left ventricular end-diastolic diameter, and left atrial diameter values were signifcantly higher in the group with lone persistent atrial fbrillation than those in the control group (7.4±3.5 ng/mL *vs* 4.3±1.2 ng/mL, p<0.0001; 3.7±1.6 mg/L *vs* 1.7±0.8 mg/L, p<0.0001; 53.0±4.2 mm *vs* 46.0±3.8, p<0.0001; 43.5±3.5 mm *vs* 33.7±3.5, p<0.0001, respectively). Serum CD40L levels were positively correlated with left atrial diameter (r=0.81, p<0.0001) and hs-CRP values (r=0.72, p<0.0001). Receiver operating characteristic curve analysis revealed that serum CD40L at the optimal cut-off level of >4.5 ng/mL successfully discriminated patients with lone atrial fbrillation from controls (area under the curve: 0.847; 95% confidence interval: 0.759–0.934; p<0.0001).
Conclusion: The present findings suggest that increased CD40L ligand levels play a crucial role in the development of lone atrial fibrillation. In addition, results support that regular clinical follow-up of these patients is necessary, due to increased risk of cardiovascular disease, determined by elevated CD40L levels.

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Although lone atrial fibrillation (AF) seen in relatively young, and healthy patients is a benign disease, development of cardiovascular disease has been demonstrated in half of these patients during long-term follow-up.[1] Literature evidence support important role of inflammation in the pathogenesis of lone AF.[2–5] In recent studies increased levels of high-sensitivity CRP which is the marker of systemic inflammation (hs-CRP) has been associated with first episode, and recurrence of lone AF.[3,6] Association between higher CRP levels, and catheter ablation with AF recurrence has been demonstrated. [7,8] Besides achievement of sinus rhythm following successful AF ablation, and subsequent and significant decrease in the concentrations of inflammatory markers as interleukin (IL)-6, CRP, and CD40 ligands were detected [9] Leftheriotis et al. observed higher CRP, CRP, tumor necrosis factor-α (TNF-α) , and intercellular adhesion molecule -1(ICAM-1) in patients with lone AF when compared with the control group. In the same study rapidly decreasing levels of IL-6, and ICAM-1 were determined as early-stage predictors of sınus rhythm achieved, and maintained in patients with lone AF within a year following cardioversion ir.[10]

CD40 ligand is a protein belonging to tumor – necrosis factor, and plays a role in the pathogenesis of atherosclerosis with its inflammatory, and prothrombotic characteristics.[11] CD40 ligand is expressed from monocytes, platelets, T-lymphocytes, endothelium, and smooth muscle cells.[11,12] In observational, and progressive studies, the role of CD40 ligand in the prediction of cardiovascular events has been demonstrated.[13,14] It has been thought that activation of platelets, and coagulation by CD40 ligand might trigger cardiovascular events via its contribution to clot formation. Clinical studies performed concerning this issue have demonstrated both the association between soluble CD40 ligand levels with increased cardiovascular events, and also its role in the prediction of thromboembolic events.[11,15,16] When the contribution of inflammation to the development of AF is taken into consideration, the possible role of CD40 ligand in the pathogenesis of AF with its inflammatory characteristics has been suggested

As far as we know, the association between CD40 ligand, and development of lone AF has not been investigated in the literature so far. Starting from this fact we have compared serum CD40 ligand levels of the patients with persistent AF, and healthy individuals in order to investigate the potential relationship between persistent lone AF, and CD40 ligand.

Abbreviations:

AF *Atrial fibrillation*
CD40L *CD40 ligand*
hs-CRP *High-sensitivity C-reactive protein*
ICAM-1 *Intercellular adhesion molecule-1*
IL *Interleukin*
TNF-α *Tümör- necrosis factor –α*
BMI *Body mass index*

METHODS

Study population

A total of 35 patients with persistent lone AF who applied to our cardiology outpatient clinic were included in our cross-sectional, and observational study.The study was performed in compliance with the principles set forth by Helsinki declaration after approval from ethics committee of Training and Research Hospital where the study was conducted (File no: 2015/185). Undersigned, and completed enlightened consent forms were obtained from all participants. Thirty healthy volunteers who applied to the cardiology outpatient clinics for check-ups constituted the control group.

Lone AF was defined as AF detected in patients aged 60 years of age who have not any present or past structural heart disease (coronary artery disease, heart failure, and cardiomyopathy), diabetes mellitus, thyroid disease, and hypertension, and any factor which may trigger arrhytmia. Besides using standard laboratory tests any hepatic, and renal dysfunction were not detected in these patients. Persistent AF was defined as type of AF which lasts for a long time, and does not terminate spontaneously, and so electrical or pharmacologic cardioversion is needed for return to a sinus rhythm.

Patients with moderate, and advanced valvular disease, hypertension, diabetes mellitus, coronary artery disease, thyroid disease, episodic or persistent AF, cardiomyopathy, heart failure, chronic renal, and hepatic failure, systemic inflammatory disease, autoimmune disease, malignant disease or infection were not included in the study.

Detailed medical histories of all the study participants, and their physical examinations were performed. All patients included in the study had lone AF at admission. Demographic, and clinical features of the patients as age, gender, body mass index (BMI), use of alcohol, and tobacco products were recorded.

Biochemical Measurements

Venous blood samples of study participants after 12 hours of fasting were drawn into citrate containing tubes without permitting stasis of the samples. All patients in the persistent lone AF group had atrial fibrillation at admission. The blood samples obtained were centrifuged at 3000 rpm for at least 20 minutes. Serum samples were kept in deep freeze at-80^{o}C till the time of analysis.

Serum CD40 ligand (CD40L) levels were measured using enzyme-linked immunosorbent assay (ELISA) method, and commercially available kit (Human Cluster of differentiation 40 ligand (CD40L) (Hangzhou Eastbiopharm Co., LTD., Hangzhou, China). The measurements were realized in line with directives provided by the manufacturing firm. Variations in intra-assay, and inter-assay coefficients as 9.7, and 11.2 % were detected respectively.

Glucose, lipid profile, creatinine values were measured from blood samples using standard laboratory methods. Serum high-sensitivity CRP (hs-CRP) levels (hs-CRP) were measured in autoanalyser using commercially available kits Abbott Architect C16200 chemistry (Abbott Laboratories, Abbott Park, IL)

Transthoracic echocardiography

Transthoracic echocardiographic procedures were performed in all study participants. Transthoracic echocardiograms were realized using standard parasternal, and apical windows while the patient was in the left oblique decubitus position Echocardiographic examinations were performed by the same cardiologist blinded to the clinical conditions of the patients using Vivid 7 Dimensions system echocardiography device (GE-Vingmed Ultrasound, Horten, Norway) with a 1.5–4.3 mHz (megaHertz) transducer.

Standard echocardiographic measurements as left ventricular end-systolic, and end-diastolic diameters, anteroposterior diameter of the left atrium, both left ventricular posterior wall thickness, and interventricular septum thickness in diastole and left ventricular ejection fraction were achieved in compliance with the recommendation stated in the guideline of American Society of Echocardiography.[17]

Statistical analysis

For statistical analyses SPSS 22.0 (Statistical Package for Windows, Chicago, IL) program was used. The normality of distribution of data was evaluated using Kolmogorov-Smirnov test. Numerical variables with normal distribution were expressed as mean ± standard deviation, while those demonstrating non-normal distribution were indicated as median, and IQR (interquartile range). Categorical variables were shown as numbers, and percentages. For the analysis of numerical variables Mann-Whitney U-test, and independent samples -t test were used. In the evaluation of categorical variables, *chi*-square test was employed. Univariate logistic regression analysis was used to determine the effects of variables on lone AF. Variables detected as significant risk factors were included in the multivariate logistic regression analysis. Spearman correlation analysis was used to investigate the presence of any correlation. The most appropriate cut-off value of CD40 ligand in the prediction of lone AF was invstigated using ROC curve analysis. In the specification of the most appropriate discriminative cut-off value for lone AF, the value closest to the point with the highest sensitivity, and specificity was determined. $P<0.05$ was accepted as the level of statistical significance.

RESULTS

Clinical characteristics, and laboratory findings of the study groups are shown in Table 1. The groups were not different with respect to age, gender, tobacco use, systolic, and diastolic blood pressure, BMI, fasting blood sugar, creatinine, uric acid, lipid profile, left ventricular end-systolic diameter, left ventricular ejection fraction, left ventricular posterior wall thickness, and interventricular septum thickness in diastole

In the persistent lone AF mean serum hs-CRP, CD40L, left ventricular end-diastolic diameter, and left atrial diameter were detected to be statistically significantly higher when compared with the control group (Table 1). In univariate logistic regression analysis serum hs-CRP, CD40L, left ventricular end-diastolic diameter were observed as significant risk factors for lone AF. However in multivariate logistic regression model serum hs-CRP, CD40L, left ventricular end-diastolic diameter were detected as independent predictors of lone AF (Table 2).

In correlation analysis mean serum CD40L levels were found to be statistically significantly, and positively correlated with mean left atrial diameter ($r=0.810$, $p<0.0001$) , and mean hs-CRP levels ($r=0.720$, $p<0.0001$) (Figures 1, and 2)

Table 1. Demographic, and clinical characteristics of the study groups

Variables	Lone AF group (n=35)	Control group (n=30)	p
Clinical variables			
Age (years)	40.9±10.00	41.5±10.10	0.804
Gender, Male, n (%)	18 (56)	20 (62)	0.762
Body mass index (kg/m^2)	25.5±2.10	26.1±2.50	0.239
Smoking , n (%)	10 (31)	13 (41)	0.793
Systolic blood pressure (mmHg)	115.3±14.40	115.8±15.10	0.924
Diastolic blood pressure (mmHg)	70.3±9.60	71.7±10.40	0.491
Duration of atrial fibrillation, days	18 (IQR: 11-34)	–	–
Echocardiographic variables			
Left ventricular end-diastolic diameter (mm)	53.0±4.20	46.0±3.80	<0.0001
Left ventricular end-systolic diameter (mm)	28.2±2.20	27.8±2.50	0.505
Interventricular septum thickness in diastole (mm)	9.5±0.90	9.5±1.00	0.961
Left ventricular posterior wall thickness in diastole (mm)	9.9±0.90	9.9±1.00	0.809
Left atrial diameter (mm)	43.5±3.50	33.7±3.50	<0.0001
Left ventricular ejection fraction (%)	58.8±4.01	59.6±2.80	0.122
Biochemical variables			
Fasting blood sugar	92 (IQR: 78-103)	93 (IQR: 70-104)	0.587
Serum kreatinin (mg/dL)	0.7 (IQR: 0.50-1.20)	0.7 (IQR: 0.5-1.03)	0.104
Total cholesterol (mg/dL)	202 (IQR: 142-257)	201 (IQR: 134-287)	0.656
High-density lipoprotein cholesterol (mg/dL)	40 (IQR: 22-53)	40 (IQR: 23-70)	0.231
Low-density lipoprotein cholesterol (mg/dL)	125 (IQR: 73-167)	120 (IQR: 83-184)	0.749
Uric acid (mg/dL)	4.8±1.33	4.7±1.52	0.715
CD40 Ligand (ng/mL)	7.4±3.50	4.3±1.21	<0.0001
High-sensitivity C-reactive protein (mg/L)	3.7±1.61	1.7±0.82	<0.0001

IQR: interquartile range

Table 2. Univariate, and multivariate regression analysis of the correlation between risk factors, and persistent sole atrial fibrillation

Variables	Univariate analysis			Multivariate analysis		
	Odds ratio	95% confidence interval	*p*	Odds ratio	95% confidence interval	*p*
Left ventricular end-diastolic diameter (mm)	0.681	0.582–0.813	0.0001	41.991	0.639–2.760	0.007
CD40L (ng/mL)	2.450	4.043–1.482	0.0001	-0.901	0.332–1.031	0.04
hs-CRP (mg/L)	0.144	0.061–0.362	0.0001	1.364	1.113–1.662	0.002

CD40L: CD40 ligand; hs-CRP: high-sensitivity C-reactive protein.

In the ROC analysis significant effectiveness of serum CD40L values in the discrimination between lone AF, and healthy control group was observed. The most appropriate threshold value for CD40L in the discrimination between groups with and without AF was determined as >4.5 ng/mL (area under curve:0.847, 95 % confidence interval: : 0.759–0.934; p<0.0001). When >4.5 ng/mL was accepted as the threshold value, its sensitivity, specificity, positive-,and negative- cut-off values were detected as 88,83,63, 67, and 86 %, respectively (Table 3).

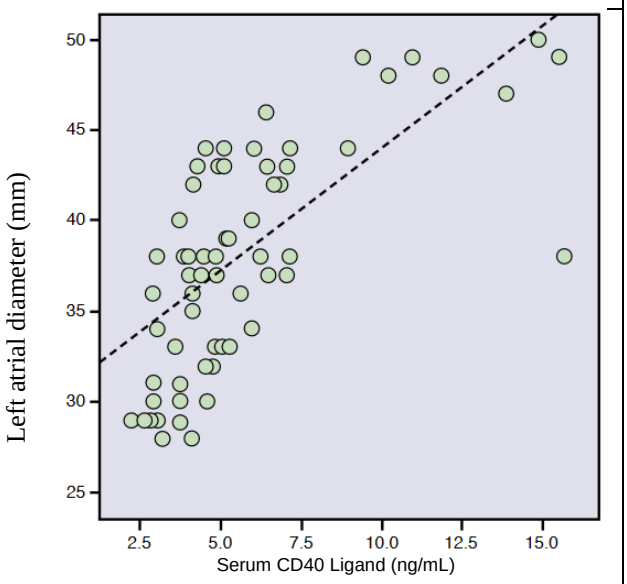

Figure 1 Correlation between the left atrial diameter, and serum CD40 ligand levels.

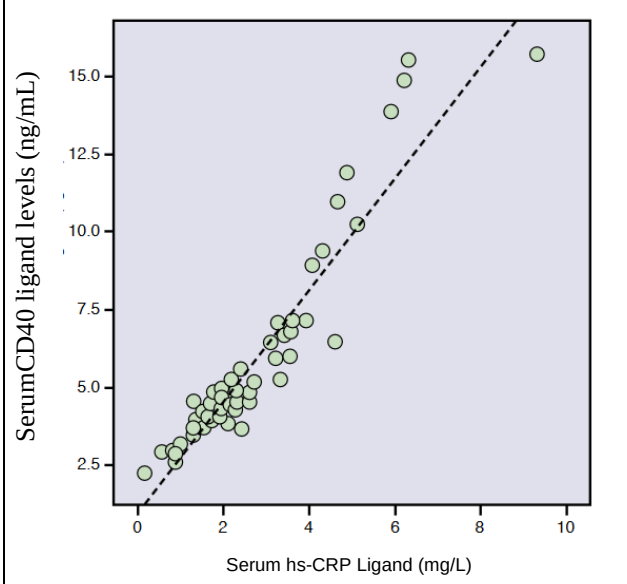

Figure 2. Correlation between serum CD40 ligand, and serum high-sensitivity C-reactive protein levels.

Table 3. Optimal serum CD40 ligand threshold value in differentiation of sole atrial fibrillation

	Cut-off Value	Sensitivity (%)	Posiitve cut-off (%)	Specificity (%)	Negative cut-off (%)	*p*
CD40 Ligand (ng/mL)	>4.5	88	67	63	86	<0.0001

DISCUSSION

In our study higher serum CD40L, and hs-CRP levels were detected in the persistent lone AF group relative to the control group A positive correlation was detected between serum CD40L levels, left atrial diameter, and hs-CRP levels. In this study for the first time it has been shown that increased serum CD40L (>4.5 ng/ml) levels can discriminate between healthy individuals and patients with persistent lone AF .

Inflammation is thought to be associated with various pathologic processes which play a role in the development of AF as oxidative stress, apoptosis, and fibrosis. Although evidence suggesting the role of inflammation in the pathophysiology of AF is available, the issue whether AF is the cause or the outcome of inflammation has not been clearly revealed yet.[18] Among persistent AF patients, decreases in hs-CRP levels in those who could achieve sinus rhythm with application of cardioversion suggest that inflammation is an outcome, rather than a cause of AF.[5]

Still the important role of inflammation in the pathogenesis of AF has been suggested. Higher levels of serum hs-CRP, and IL-6 were detected in both new-onset, and chronic AF patients relative to the control group.[19] Inflammation is thought to effect electrical, and structural remodelling of atrium possibly contributing to the onset, and maintenance of arrhytmia. Concentrations of osteoprotegrin which is another biomarker of inflammation has been associated with community-acquired cases with AF.[20]

Recent studies have suggested the presence of a correlation between inflammation, and emergence, and maintenance of lone AF. In a study by Frustaci et al. histologically detected abnormalities were demonstrated in atria of lone AF patients. Most of these histological abnormalities consisted of inflammatory infiltrations associated with foci of myocytic necrosis, and in 66 % of the patients histopathological finding were found to be consistent with mycarditis.[2]

Higher levels of inflammation, and oxidative stress biomarkers as CRP, TNF-α, sICAM-1, IL-6, malon-dialdehyde, and nitrothyrosine were detected in patients with lone AF relative to the control group. Besides, association between recurrence of lone AF, and IL-6, sICAM-1, malondialdehyde, and nitrothyrosine was found. These results suggest the critical role of inflammation, and oxidative stress in the development of lone AF.[10] Significantly higher hs-CRP levels were detected in patients who for the first time experienced paroxysmal AF episodes when compared with the control group.[6] Canpolat et al. detected higher plasma hs-CRP, and fibronectin levels in patients with paroxysmal lone AF relative to the control group. In the same study, plasma fibronectin, and hs-CRP levels were detected as independent predictors in the electrical remodelling of the left atrium. In patients with lone AF, biomarkers of fibrosis, and inflammation were found to be correlated with structural, and electrical remodelling of the atrium.[21] In support of this study, the results of the study by Zheng indicated the important role of inflammation in electrophysiologic remodelling of atrium which predisposes the patient to AF.[22]

Recent studies have indicated potential role of CD40L which is a proinflammatory, and prothrombotic molecule in the pathophysiology of AF, and also pointed to its probable responsibility in thrombotic complications which developed in patients with AF.[11,23] Increasing levels of serum CD40L prior to off-pump bypass surgery have been observedly associated with postoperatively increased development of AF independent from other risk factors..[24] Besides, Osmancik et al.. noted decrease in IL-6, CRP,and CD40L concentrations in patients who achieved sinus rhythm after successful AF ablation..[9] As a known fact, CD40L levels increase in AF patients.[18] However as far as we know, literature data which indicate higher CD40L levels in AF patients relative healthy control group are lacking. In our study for the first time higher serum CD40 L levels were found in patients with persistent lone AF in comparison with healthy control group. Starting from this point, one can say that increased serum CD40L levels contribute to the development of lone AF.

Left atrial, and ventricular end-diastolic diameters , and hs-CRP were found to be correlated with lone AF.[22] Luan et al. demonstrated that levels of IL-18 which is a pleiotrophic proinflammatory cytokine increased in lone AF patients, and indicated the presence of a positive correlation between left atrial diameters, and levels of IL-18.[25]

Also in our study, left atrial diameter, hs-CRP, and CD40L levels were higher in patients with lone AF when compared with healthy volunteers, and a positive correlation was detected between CD40L levels, left atrial diameter, and hs-CRP levels.

In studies performed it has been demonstrated that CD40L levels predict stroke in patients with AF, and it can discriminate AF patients with extravalvular abnormalities carrying high risk of thromboembolism.[11,16] Significantly higher CD40L levels were detected in patients with atrial fibrillation relative to healthy control group. In the same study a significant difference was not detected between healthy, and diseased groups with respect to platelet surface CD40L levels, and total CD40L levels per platelet. It was also emphasized that CD40L-related indices failed to identify AF patients carrying a higher risk for stroke..[26] Though serum CD40 ligand levels have been demonstrated to be clinical markers of inflammation, its correlation with left atrial size could not be determined.[27] In our study which differed from these studies it was shown that CD40L levels were higher relative to healthy volunteers, and also the presence of a direct correlation between serum CD40L levels, and left atrial diameters was also indicated in patients with persistent AF. Results of our study do not prove the existence of a cause-effect relationship between serum CD40 ligand levels, and development of lone AF. Findings of this study suggest the critical role of inflammation, and CD40 ligand in the pathogenesis of inflammation. Our study also indicates important contribution of CD40L to the pathogenesis of AF in addition to its role in thromboembolic events.

Since diagnosis of paroxysmal lone AF can only be possible with detection of an AF episode, diagnosis of these patients is more difficult. Though our study was performed in patients with persistent AF, our findings suggest that serum CD40L levels can discriminate between patients with paroxysmal lone AF and healthy individuals which will facilitate diagnostic process of these patients Therefore our findings suggest the necessity of performing large-scale studies which will investigate the possible role of CD40L level in the diagnosis of the patients with paroxysmal lone AF.

Our study has some limitations which should be mentioned. The number of patients included in the study is relatively small. Our studies should be supported with well-designed, large-scale studies. Inflammation biomarkers of the patients were measured only once. Therefore fluctuations in the levels of biomarkers were not observed. Another limitation of the study is that another group with lone paroxysmal AF was included in the study, while diagnostic value of CD40L was not tested in these patients. Measurements of biomarkers of inflammation in blood do not directly reflect inflammation in the atrial tissue. Finally, other parametres, and biomarkers associated with inflammation could be analyzed in our study.

Firstly in our study, significantly higher serum CD40L levels were detected in patients with persistent lone AF when compared with healthy volunteers. Findings of our study suggest that CD40 ligand may play a critical role in the development of lone AF. In conclusion, electrophysiologic, and structural changes triggered by inflammation may play a role in the pathogenesis of lone AF. Thus, in fact, it has been suggested that lone AF is not totally innocent, and carries a risk for cardiovascular diseases Therefore, regular follow-up of these patients is important, and necessary regarding their clinical characteristics, and risk factors.

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